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(54) Title: DEVICES AND METHODS IN INTRACEREBROSPINAL DELIVERY OF MORPHINE-6-GLUCURONIDE

(57) Abstract:

DEVICES AND METHODS IN INTRACEREBROSPINAL DELIVERY OF MORPHINE-6-GLUCURONIDE

FIELD OF THE INVENTION

The invention relates to drug delivery devices in the administration of drugs to the central nervous system.

BACKGROUND OF THE INVENTION

Morphine is the opioid drug of choice for management of chronic pain. This preference for morphine is due at least in part to its low cost, the ability of the drug to provide relief from pain of a variety of origins, and the vast experience with this drug. Despite the apparent advantages of morphine, many experts in pain management believe that morphine and other narcotics are under-prescribed for chronic pain patients.

One major reason for hesitancy in prescription of opioids such as morphine is the risk of the side effects associated with long-term administration. Examples of such side effects include, but are not necessarily limited to, severe reduced cough reflex, bronchial spasms, release of histamine, stimulated release of adrenalin, nausea, vomiting, peripheral vasodilation, orthostatic hypotension, vagal impact on the heart, contraction of smooth muscles (sphincters), reduced peristaltic motility in the gastrointestinal tract and associated constipation, urinary retention, changes in the regulation of body temperature and sleep pattern, as well as the development of opioid tolerance and addiction. Patients who develop opioid tolerance require increased doses to achieve a satisfactory analgesic effect, and risk the development of further undesirable side effects such as respiratory depression, which can be life threatening. Discontinuing opioid administration in a dependent subject results in the onset of withdrawal symptoms, which itself can be severely painful.

Where the concerns regarding side effects might be outweighed by the serious need for pain relief as in terminally ill patients, many doctors still avoid prescribing narcotics due to their concerns of the abuse of surplus medication by others in contact with the patient, or are even concerned that their frequent prescription of the drug might lead to criminal investigation. As a result, many chronic pain patients do not receive the best available therapy despite the fact that such is readily available.

After systemic administration (*e.g.*, oral, subcutaneous, intravenous, *etc.*), morphine is metabolized. About 90% of morphine is converted to its metabolites, principally by

glucuronidation. Approximately 45-55% of morphine is metabolized to morphine-3-glucuronide (M3G) and another 10-15% is metabolized to morphine-6-glucuronide (also known as morphine-6β-glucuronide or glucuronic acid-6-(7,8-didehydro-4,5 epoxy-17-methylmorphinan-3,6 diolyl) ester; referred to herein as M6G). Other minor metabolites include morphine-3,6-diglucuronide, morphine-3-ethereal sulphate, normorphine, normorphine-6-glucuronide, normorphine-3-glucuronide, and codeine (for a review see Christrup (1997) *ACTA Anaesth. Scand.* 41:116-122). Of these metabolites, M6G binds opioid receptors (predominately the μ receptor), exhibits analgesic properties, and appears in plasma in clinically relevant levels following systemic administration of morphine. However, the metabolism of morphine, as well as the influence of morphine metabolites upon the morphine's pharmacodynamics, are still not clearly understood and have only been subjected to limited investigation, particularly in situations of chronic use (see, *e.g.*, Christrup, *supra*; Kalman *et al.* (1997) *Reg. Anesth.* 22:131-6; and Samuelsson *et al.* (1993) *Pain* 52:179-85).

In recent years, interest in delivery of M6G to control pain in human subjects has increased. Systemic routes for delivery of M6G have included transdermal delivery (see, *e.g.*, U.S. Pat. No. 5,705,186) and nasal delivery (see, *e.g.*, U.S. Pat. No. 5,629,011). Central administration (*e.g.*, intraspinal or intracerebroventricular delivery) of a bolus of M6G to human subjects has also been described, though to a lesser extent. Grace *et al.* ((1996) *Anesth. Analg.* 83:1055-9) described delivery of an intrathecal bolus of M6G for control of post-operative pain following total hip replacement, although this group did not observe any improvement in side effects relative to intrathecal morphine. Morley *et al.* ((1992) *Lancet* 340:1045) described that administration of an intrathecal bolus of M6G to one patient resulted in full relief from pain associated with disseminated colonic carcinoma. Hanna *et al.* ((1990) *Br. J. Anaesth.* 64:547-50) reported that delivery of a bolus of M6G through an intrathecal catheter provided greater analgesic activity than delivery of morphine by the same route and with an equivalent incidence of side effects. However, the conclusions of Hanna *et al.* were later criticized (Hardy (1991) *Br. J. Anaesth.* 66:271-4). Not all reports of pain relief following central administration of M6G have been positive. For example, in one study administration of a bolus of intrathecal M6G followed by bupivacaine caused profound, delayed respiratory depression in opioid-naive subjects (Coe *et al.* (1992) *Br. J. Anaesth.* 69:221P).

As is evident from the above, while M6G has the potential to be a drug of choice for management of chronic pain, no conventional protocol for safe, effective administration that is

associated with an acceptable range of side effects is available. The present invention addresses this problem.

SUMMARY OF THE INVENTION

The invention features a method for management of chronic pain by intracerebrospinal delivery of morphine-6-glucuronide (M6G) or a bioactive derivative thereof. In various embodiments, the invention involves delivery of M6G or a derivative thereof in a patterned fashion (*e.g.*, substantially continuous delivery) and/or at a relatively low volume rate, . Drug delivery can be accomplished using an external or implanted pump, preferably an implanted pump.

A primary object of the invention is provide a method for convenient, long-term intracerebrospinal delivery of M6G.

Another object of the invention is to effectively treat conditions associated with pain by administration of M6G at a relatively low volumetric rate, so as to provide the drug in a therapeutically effective amount (*e.g.*, in an amount adequate to provide the subject relief from pain symptoms associated with the condition).

Delivery of a relatively low volume rate and/or dose of M6G, particularly a substantially constant, low volume rate and/or low mass dose, can provide for an improvement in adverse side effects that can be normally associated with delivery of opioid analgesics. Given the adverse effects of opiate analgesics, this advantage is of considerable benefit to those requiring pain relief, particularly in relatively long term (*e.g.*, 1-4 weeks and longer) or chronic pain situations. Furthermore, low volume delivery and/or low dose delivery is more cost-effective in that it requires a smaller volume of drug formulation and less drug for the selected treatment period, which in turn increases the period of time between refilling of the drug reservoir. The method of the invention can thus make effective pain management therapy available to a broader population.

The invention is also advantageous in that it facilitates delivery of M6G, a morphine derivative that, due to its potency, is less amenable to safe and effective delivery using conventional methods (*e.g.*, bolus intraspinal injection). The present invention can be provided so as to accomplish consistent delivery of M6G at low dose and/or low volume rates (*e.g.*, on the order of nanoliters to milliliters per day) thereby eliminating the undesired overdosing and underdosing inherently associated with bolus administration to provide safe, effective therapy while minimizing the risk of undesirable side effects.

Where the method uses an implantable device, the invention has the additional advantage that it avoids the need for placement of external needles and/or external catheters in the subject,

which provides sites subject to infection. In addition, use of an implanted device increases patient compliance with a prescribed therapeutic regimen, and substantially decreases or completely avoids the risk of abuse or overdose of the drug.

Another advantage of the invention is that delivery using an implantable drug delivery device affords greater mobility and easier outpatient management. Furthermore, where M6G is delivered at low volume rates, the reservoir of the drug delivery device can be smaller and/or refilled or replaced less frequently. These features further enhance the patient's comfort, convenience, and compliance and reduce the burden on the medical caretakers.

Delivery of M6G according to the invention is advantageous over bolus delivery in several respects. As noted above, in a bolus injection the entire drug formulation volume is delivered at once, and thus is usually associated with overdosing and underdosing of drug. Bolus administration is associated with overdosing because a larger than therapeutically effective amount of drug must be administered if the drug is to last until the next bolus dose. Bolus administration is also associated with underdosing because the amount of drug present in the subject may be less than the therapeutically effective amount just prior to administration of the next bolus. In addition, where drug delivery by bolus administration requires delivery of a relatively large volume of formulation, bolus administration can result in local tissue damage, and/or changes in the composition of the body fluid or tissue into which the drug is delivered (*e.g.*, changes in CSF composition). Delivery according to the invention avoids these problems in that, for example, the required volume of drug formulation can be delivered over a longer period of time. The delivery method of the invention thus minimizes disturbance of tissue at the delivery site (*e.g.*, the dura, epidural space, intrathecal (*i.e.*, subarachnoid) space, *etc.*), which in turn minimizes or avoids adverse tissue reactions (*e.g.*, edema). In addition, delivery according to the invention yields more reproducible drug absorption and distribution into the body without inflicting local tissue damage, and provides optimal drug dosing. Furthermore, because the catheter used to facilitate low volume rate drug delivery is generally of relatively small dimensions (*e.g.*, on the order of 0.1 mm to about 6 mm outer diameter or, in some embodiments, even smaller), the degree of invasion and disturbance of tissues in order to access the intracerebrospinal delivery site is minimized (*e.g.*, the size of puncture in the dura to access the subarachnoid space for intrathecal delivery is relatively small).

The invention is also advantageous in that delivery directly to an intracerebrospinal site allows for delivery of concentrated drug doses to the site at which therapy is needed while

reducing the risk of side effects normally associated with systemic delivery of therapeutically effective doses of M6G.

The invention is also advantageous in that delivery according to the invention exploits the hydrophilicity of M6G, which facilitates retention of the drug in the cerebrospinal fluid. The invention also takes advantage of M6G's analgesic potency after intracerebroventricular or intrathecal administration relative to the parent molecule (*e.g.*, an analgesic potency anywhere from 45 to 800 times greater than that of morphine).

The invention is also advantageous in that it involves delivery of a drug that is not metabolized following administration according to the invention, thus making delivery of an effective dose more predictable.

These and other objects, advantages and features of the present invention will become apparent to those persons skilled in the art upon reading the details of the methodology and compositions as more fully set forth below.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 illustrates delivery of M6G using an implantable pump connected to a drug delivery catheter positioned for delivery of drug to an intracerebrospinal site, exemplified here by a site in the intrathecal space.

Fig. 2 is a schematic providing a cut-away view of a catheter distal end positioned within the spine for intrathecal delivery of M6G.

Fig. 3 is a schematic of a partial cut-away view illustrating delivery to an intracerebrospinal site, here exemplified by an intracerebroventricular site in the brain, according to the invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Before the present methods, devices, and compositions for intracerebrospinal delivery of M6G are described, it is to be understood that this invention is not limited to the specific methodology, formulations, and conditions susceptible to therapy described as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a", "and", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for

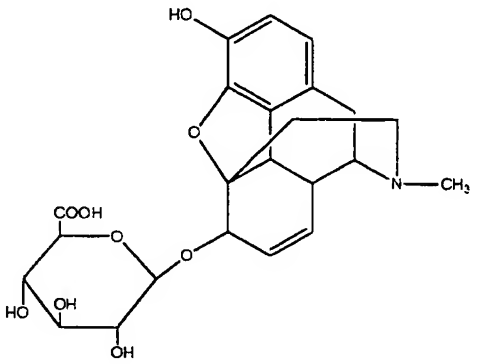
example, reference to "a drug delivery device" includes a plurality of such devices and reference to "the method of delivery" includes reference to equivalent steps and methods known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs. Although any methods, devices and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, the preferred methods, devices and materials are now described.

All publications mentioned herein are incorporated herein by reference for the purpose of describing and disclosing the compositions and methodologies which are described in the publications which might be used in connection with the presently described invention. The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such a disclosure by virtue of prior invention.

Definitions

The term "morphine-6-glucuronide" (referred to herein as M6G) is meant to refer to a compound of the formula:



as well as pharmaceutically acceptable salts thereof suitable for intracerebrospinal administration.

"M6G derivative" is meant to refer to a bioactive derivative of M6G produced by either natural and/or synthetic processes, as well as pharmaceutically acceptable salts thereof suitable for administration according to the invention.

The term "subject" is meant any subject, generally a mammal (*e.g.*, human, canine, feline, equine, *etc.*), to which delivery of M6G for management or control of pain, particularly chronic pain, is desired.

The term "therapeutically effective amount" is meant an amount of a therapeutic agent, or a volumetric or mass rate of delivery of a therapeutic agent, effective to facilitate a desired therapeutic effect, *e.g.*, alleviation of pain. The precise desired therapeutic effect (*e.g.*, the degree of pain relief, and source of the pain relieved, *etc.*) will vary according to the condition to be treated (*e.g.*, the condition with which chronic pain is associated), the formulation to be administered, and a variety of other factors that are appreciated by those of ordinary skill in the art. In general, the method of the invention involves the suppression or mitigation of pain in a subject suffering from pain that may be associated with any of a variety of identifiable or unidentifiable etiologies.

The term "implantation site" is used to refer to a site within the body of a subject at which a drug delivery device is introduced and positioned.

"Delivery site" as used herein is meant to refer to an area of the body to which drug is delivered. A delivery site within the spine is of particular interest in the present application, *e.g.*, epidural, subdural, intrathecal, and the like.

"Drug delivery device" as used herein is meant to encompass any device, suitable for delivering a formulation to an intracerebrospinal site according to the invention, particularly a device adapted for complete or partial implantation. "Drug delivery device" encompasses devices that are partially, substantially completely, or completely implanted. "Pump" is used herein to refer to convective delivery systems in general. "Drug delivery device" thus encompasses any device with any mechanism of action suitable for use in the invention, including diffusive, erodible, or convective systems, e.g., osmotic pumps, biodegradable implants, electrodiffusion systems, electrochemical systems, electroosmosis systems, vapor pressure pumps, electrolytic pumps, effervescent pumps, piezoelectric pumps, erosion-based systems, or electromechanical systems. Convective drug delivery devices are of particular interst.

The term "controlled drug delivery device" is meant to encompass any device wherein the release (e.g., rate, timing of release) of a drug or other desired substance contained therein is controlled by or determined by the device itself and not the environment of use.

"Patterned" or "temporal" as used in the context of drug delivery is meant delivery of drug in a pattern, generally a substantially regular pattern, over a pre-selected period of time (*e.g.*, other than a period associated with, for example a bolus injection). "Patterned" or "temporal" drug delivery is meant to encompass delivery of drug at an increasing, decreasing, substantially constant, or pulsatile, rate or range of rates (*e.g.*, amount of drug per unit time, or

volume of drug formulation for a unit time), and further encompasses delivery that is continuous or substantially continuous, or chronic.

By "substantially continuous" as used in, for example, the context of "substantially continuous delivery", is meant to refer to delivery of a substance (*e.g.*, a drug) in a manner that is substantially uninterrupted for a pre-selected period of drug delivery (other than a period associated with, for example, a bolus injection). Furthermore, "substantially continuous" drug delivery can also encompass delivery of drug at a substantially constant, pre-selected rate or range of rates (*e.g.*, amount of drug per unit time, or volume of drug formulation for a unit time) that is substantially uninterrupted for a pre-selected period of drug delivery.

By "low volume rate" as used herein with reference to intracerebrospinal delivery of M6G is generally meant a volume rate of from about 10 nl/day to about 2 ml/day, generally from about 40 nl/day to about 1 ml/day, usually about 0.2 µl/day to about 0.5 ml/day, typically from about 1.0 µl/day to about 10 µl/day. The actual volume rate may vary according to the specific intracerebrospinal site selected.

The term "pain management or treatment" is used here to generally describe regression, suppression, or mitigation of pain so as to make the subject more comfortable as determined by subjective criteria, objective criteria, or both. In general, pain is assessed subjectively by patient report, with the health professional taking into consideration the patient's age, cultural background, environment, and other psychological background factors known to alter a person's subjective reaction to pain.

"Treatment" as in is used herein to encompass, but not necessarily be limited to, a decrease in severity of symptoms (*e.g.*, to provide partial or complete relief of pain) as well as management of a condition (*e.g.*, suppression of a symptom and/or correction of a defect associated with a condition to make the condition more tolerable for the subject (*e.g.*, to decrease the severity or incidence of severe episodes of pain to improve the subject's quality of life, *etc.*).

The term "proximal end" (or "first end") is used herein in connection with components and/or elements of the devices used herein that are closer to a clinician or other individual who is using the catheter and/or devices according to the invention in a medical treatment setting. Conversely, the term "distal end" (or "second end") is used herein in connection with components and/or elements that are closer to the treatment site within the body of the subject being treated.

The invention will now be described in more detail.

INTRACEREBROSPINAL DELIVERY OF M6G

The present invention is based on delivery of morphine-6-glucuronide (M6G) or a derivative thereof to an intracerebrospinal site in a manner that accomplishes administration of a therapeutically effective amount of drug (*e.g.*, an amount of M6G effective to alleviate pain) while avoiding or mitigating side effects that can be associated with bolus administration of the drug, and minimizing trauma or damage to the CNS. It should be noted that where reference is made to M6G in the disclosure herein, such reference is intended to encompass delivery of active derivatives of M6G unless specifically noted otherwise. In one embodiment, M6G is delivered in a patterned fashion, (*e.g.*, by substantially continuous delivery or other pattern other than, for example, single bolus delivery). In another embodiment, M6G is delivered at a relatively low volume rate.

In general, the methods of the invention involve delivery where M6G is not released from an implanted or external reservoir of drug as a single bolus dose, but rather is introduced into the intracerebrospinal site over time, generally gradually over time. The invention thus provides for delivery of M6G so that a desired therapeutic effect (*e.g.*, at least some degree of pain relief) is maintained in the subject for a selected period of time, while, for example, avoiding side effects that can be associated with bolus delivery of M6G. In one embodiment, M6G is delivered so that a therapeutically effective concentration of M6G is maintained within the target tissue of the subject over the desired treatment period, *e.g.*, without overdosing or underdosing. The methods of the invention can thus be carried out to avoid drug concentration "peaks" that can be associated with overdosage, as well as drug concentration "valleys" that can be associated with underdosage. The invention can thus be carried out so that drug is delivered in an amount just above the sub-therapeutic/therapeutic threshold to provide for partial or complete pain relief. In one aspect, the invention involves maintaining the concentration of drug within a therapeutically effective range in the subject's cerebrospinal fluid at or in the area of the intracerebrospinal administration site over a pre-selected period, which period can range from hours to days to weeks, months, or years depending on the duration of therapy.

Delivery of M6G according to the invention can be accomplished using a drug delivery device and an attached catheter. The catheter comprises a proximal end for permanent or removable attachment to the drug delivery device, and an implantable distal end for implantation at the desired intracerebrospinal delivery site. Drug is delivered to the intracerebrospinal site by implanting a distal end of the drug delivery catheter at the selected delivery site, and delivering M6G from a drug delivery device attached to the proximal end of the catheter, through a lumen

defined by the catheter, and to the intracerebrospinal site adjacent the catheter distal end. In all embodiments, at least the distal end of the catheter is implanted. In other embodiments, the catheter is substantially completely implanted and attached to an external or partially implanted drug delivery device. Alternatively, the catheter and drug delivery device can be fully implanted.

"Intracerebrospinal delivery site" is meant to include any site that allows access to the cerebrospinal fluid and/or access to spinal nerve roots. Intracerebrospinal delivery sites include, but are not necessarily limited to, intrathecal (*e.g.*, a delivery site within the subarachnoid space), epidural (*e.g.*, a delivery site within the extradural space) or intracerebroventricular, with intrathecal being preferred. For intraspinal delivery, the drug delivery catheter can be positioned for delivery to the intracerebrospinal delivery site by threading the catheter between vertebrae of the spine anywhere along the neuraxis from cervical to sacral vertebrae. In some embodiments, it may be preferable to access intracerebrospinal delivery sites for intraspinal delivery by placement of the catheter between the vertebrae L1 and L2, L2 and L3, L3 and L4, or L4 and L5.

The drug delivery catheter can be anchored at the intracerebrospinal delivery site so as to minimize or avoid movement of the distal end of the catheter either within the space defining the delivery site and/or to minimize the risk of dislodging the catheter from the delivery site.

Referring now to the figures, Figs. 1 and 2 illustrate one embodiment of the invention in which drug is delivered from an implanted drug delivery device **10** to an intracerebrospinal site, exemplified here by an intrathecal site. In this example, the drug delivery device **10** is positioned on the patient's back **5**, and can be either implanted beneath the patient's skin as illustrated, or retained at an external site. A formulation comprising M6G is delivered from device **10**, into the attached proximal end **21** of catheter **20**, through a lumen of catheter **20**, and out catheter distal end **22** adjacent a delivery site within the spine **15**.

Fig. 2 illustrates placement of catheter **20** within the intrathecal space of the spine. Catheter **20** is inserted through the dura **50** so that the distal end of the catheter **20** is positioned within the subarachnoid space **60**.

Fig. 3 illustrates placement of catheter **20** within an intracerebroventricular site. In this example, a distal end of catheter **20** of drug delivery device **10** is positioned for delivery of drug to a site within the brain, here exemplified as ventricle **590**. In general, drug release device **30** is completely or partially implanted at a convenient subcutaneous implantation site **500**, exemplified in Fig. 3 as a subcutaneous site along the back of the subject's neck or on the subject's back. The body of catheter **20** is implanted under the skin **560** and extends beneath the skin **560** from the implanted drug release device **30** at implantation site **500** to an access site provided in the skull

570 through which the catheter **20** is inserted for positioning of the distal end within a ventricle **590**.

Methods for implanting or otherwise positioning a drug delivery device or for implanting a catheter for intracerebrospinal delivery are well known in the art. In general, placement of the drug delivery device will be accomplished using methods and tools that are well known in the art, and performed under aseptic conditions with at least some local or general anesthesia administered to the subject. Removal and/or replacement of drug delivery devices can also be accomplished using tools and methods that are readily available.

M6G can be delivered to an intracerebrospinal site of the subject according to the method of the invention for any desired period of time. In general, intracerebrospinal administration of M6G can be sustained for several hours, to several days, to several months or years (*e.g.*, delivery can be chronic, as opposed to single-dosage bolus injection). Typically, delivery can be continued for a period ranging from about 1 month to about 12 months or more. This extended period of drug delivery is made possible by the ability of the invention to provide both therapeutic benefit (*e.g.*, relief from symptoms associated with a condition, *e.g.*, pain relief), while avoiding the onset or severity of side effects that can be associated with conventional methods of long-term intracerebrospinal drug delivery, particularly long-term delivery of an opioid analgesic.

Side effects that can be avoided or mitigated by intracerebrospinal delivery according to the methods of the invention include those associated with cytotoxicity of the drug or other drug formulation component, nausea, vomiting, confusion, respiratory depression, constipation, urinary retention, *etc.*). In addition, the methods and devices of the invention can also serve to mitigate side effects associated with delivery of any drug formulation (*e.g.*, side effects associated with disturbance of the tissues at the site of implantation, with disturbance at the site of drug delivery, fluctuations in CSF volume due to the volume of drug formulation delivered or leakage of CSF (*e.g.*, spinal headaches) *etc.*). The mitigation or avoidance of the latter types of side effects can be attributed at least in part to the small dimensions of the drug delivery catheter and to the low mass dose and/or low volume delivery rate used to accomplish drug delivery to the CNS. For example, since the invention can be carried out with low volumes of drug and small diameter catheters, the risk of incidence of spinal headaches is diminished.

The actual dose of M6G delivered will vary with a variety of factors including physical characteristics of M6G and the manner in which it is formulated for delivery (*e.g.* potency, *etc.*), the intracerebrospinal delivery site, the condition to be treated, *etc.* For example, intrathecal delivery of M6G can be accomplished at a rate of, for example, from about 0.02 μg/hr to about

5000 μg/day, or about 0.02 μg/hr to about 200 μg/hr. Appropriate amounts of drug to be delivered can be readily determined by the ordinarily skilled artisan.

Delivery of M6G according to the invention can be accomplished using a drug delivery device attached to a catheter. The distal end of the catheter is implanted at the intracerebrospinal delivery site. The proximal end of the catheter is attached to the drug delivery device to allow for flow of drug from a drug reservoir of the drug delivery device to the catheter distal end adjacent the selected intracerebrospinal delivery site. In one embodiment, the drug delivery is an external or implanted pump, with an implanted pump being preferable. Use of such drug delivery devices provides at least the following additional advantages: (1) the therapeutic effect of the drug can be provided in a chronic or continuous fashion (*e.g.*, for a relatively long period of time, *e.g.*, hours to days); (2) drug can be delivered to the subject in a smooth and consistent fashion (*e.g.*, the bolus effect is substantially avoided, *e.g.*, both at the initiation of therapy and/or throughout the pre-selected period of therapy); (3) the potential for misuse or abuse of the drug is substantially diminished (*e.g.*, decreased risk of dependency, no or little access to a surplus of drug, etc.); (4) the risk of overdosing and resulting toxic reactions are decreased (*e.g.*, risk of overdose due to patient or health professional error during administration is avoided); and (5) patient compliance is increased (*e.g.*, the device ensures that drug is continually administered throughout the pre-selected therapeutic period).

Drug delivery devices, catheters, conditions susceptible to treatment, and formulations suitable for use in the present invention are described in further detail below.

DRUG DELIVERY DEVICES AND CATHETERS

Any of a variety of drug delivery devices and catheters can be used in the present invention *to* accomplish delivery of a drug according to the invention.

Controlled drug release Devices

Any of a variety of drug delivery devices are suitable for use in the present invention. In general, the drug release devices suitable for use in the invention comprise a drug reservoir for retaining a drug formulation. The drug delivery device can be selected from any of a variety of drug release devices that are conventionally used as an external element (*e.g.*, an external pump) or implanted element of a drug delivery system. In a preferred embodiment, the drug release device is a controlled drug release device. The term "controlled drug release device" is meant to encompass any device that provides for controlled release of a drug or other desired substance, and that can be adapted for use in the methods and devices of the invention, *e.g.*, a drug delivery device

that provides for controlled release of drug through a catheter to a selected delivery site, and at a rate that is suitable to accomplish delivery of a therapeutically effective amount of drug to a treatment site according to the methods of the invention. Exemplary drug release devices suitable for use with the drug delivery devices can be based on either diffusive systems (*e.g.*, electrodiffusion systems, electroosmotic systems, erosion-based systems, and the like) or convective systems (*e.g.*, electromechanical pumps, osmotic pumps, vapor pressure pumps, electrolytic pumps, effervescent pumps, piezoelectric pumps, and the like).

Controlled release of drug from the drug delivery device reservoir can be accomplished in any of a variety of ways according to methods well known in the art, *e.g.*, by incorporation of drug into a polymer that provides for substantially controlled diffusion of drug from within the polymer, use of an osmotically-driven device, etc. Drug can be delivered from the drug delivery device and through the drug delivery catheter to the delivery site as a result of capillary action, or as a result of diffusion or convection.

In one embodiment, the drug release device is a controlled drug release device in the form of an osmotically-driven device. Preferred osmotically-driven drug release systems are those that can provide for release of drug in a range of rates of from about 0.01 μl/day to about 100 μl/day (*e.g.*, from about 0.0004 μl/hr to about 4 μl/hr), preferably from about 0.04 μl/day to about 10 μl/day, generally from about 0.2 μl/day to about 5 μl/day, typically from about 0.5 μl/day to about 1 μl/day. In one embodiment, the volume/time delivery rate is substantially constant and at a substantially consistent rate (*e.g.*, delivery is generally at a rate ± about 5% to 10% of the cited volume over the cited time period, *e.g.*, a volume rate of about 10 μl/day is accomplished by delivery of about 800 μl/hour over a period of 24 hours, with the delivery rate over that 24 hours period fluctuating over that period by about ± 5% to 10%). Exemplary osmotically-driven devices suitable for use in the invention include, but are not necessarily limited to, those described in U.S. Pat. Nos. 3,760,984; 3,845,770; 3,916,899; 3,923,426; 3,987,790; 3,995,631; 3,916,899; 4,016,880; 4,036,228; 4,111,202; 4,111,203; 4,203,440; 4,203,442; 4,210,139; 4,327,725; 4,627,850; 4,865,845; 5,057,318; 5,059,423; 5,112,614; 5,137,727; 5,234,692; 5,234,693; 5,728,396; and the like. In one embodiment the controlled drug release device is an osmotic pump, *e.g.*, an osmotic pump similar to that described in U.S. Pat. No. 5,728,396. In one embodiment of particular interest, the osmotic pump is a DUROS™ osmotic pump.

Drug delivery catheter

The catheter used in the drug delivery system suitable for use in the invention is generally an elongate, substantially hollow structure having a proximal end associated with the drug delivery device of the drug delivery device, and a distal end for delivery of M6G to a desired delivery site. The proximal end of the catheter is associated with or attached to the drug delivery device so that drug in the drug reservoir of the delivery device can flow from the drug delivery device, into and through the catheter, and out the distal catheter end adjacent the intracerebrospinal delivery site.

The drug delivery catheter comprises a lumen having a diameter that can be equal to, or can be greater or less than, the diameter of the drug delivery device orifice that serves as a drug reservoir outlet, with the proviso that the catheter is attached in a manner that avoids leakage of drug out of the drug delivery system. Where the drug delivery device dispenses drug by convection (as in, *e.g.*, osmotic drug delivery systems), the orifice size as well as the size of the lumen of the drug delivery catheter leading from the reservoir of the drug release system can be designed as described by Theeuwes (1975) *J. Pharm. Sci.* 64:1987-91.

The catheter body can be of any of a variety of dimensions and geometries (*e.g.*, curved, substantially straight, tapered, *etc.*), that can be selected according to their suitability for the intended intracerebrospinal delivery site. The distal end of the catheter may provide a distinct opening for delivery of drug or a plurality of openings. The outside diameter of the catheter body can be of a variety dimensions, for example in the range of from about 0.1 mm to 6 mm, usually being in the range from about 0.125 mm to about 1 mm. The catheter body will define an inner lumen that can likewise be of a variety of sizes, for example having an inner diameter in the range of from about 0.005 mm to 5 mm, usually being in the range from about 0.025 mm to 1 mm, with catheters having larger outside diameters usually having larger lumen diameters.

The catheter may be produced from any of a variety of suitable, substantially impermeable materials. Exemplary catheter body materials include, but are not necessarily limited to, polymers; metals; glasses; polyolefins (high density polyethylene (HDPE), low density polyethylene (LDPE), linear low density polyethylene (LLDPE), polypropylene (PP), and the like); nylons; polyethylene terephtholate; silicones; urethanes; liquid crystal polymers; PEBAX™; HYTREL™; TEFLON™; perflouroethylene (PFE) perflouroalkoxy resins (PFA); poly(methyl methacrylate) (PMMA); multilaminates of polymer, metals, and/or glass; nickel titanium alloy (*e.g.*, NITINOL™); and the like. The catheter can comprise additional materials or agents (*e.g.*, coatings on the external or internal catheter body surface(s)) to facilitate placement of the catheter and/or to provide other desirable characteristics to the catheter. For example, the catheter inner and/or outer walls can be

coated with silver or otherwise coated or treated with antimicrobial agents, thus further reducing the risk of infection at the site of implantation and drug delivery.

In one embodiment, the catheter is primed with a drug-comprising formulation, *e.g.*, is substantially pre-filled with drug prior to implantation. Priming of the catheter reduces delivery start-up time, *i.e.*, time related to movement of the drug from the drug delivery device to the catheter distal end. This feature is particularly advantageous in the present invention where drug is delivered at relatively low volume rates.

CONDITIONS AMENABLE TO TREATMENT BY INTRACEREBROSPINAL DELIVERY OF M6G

In general, the invention can be used to administer M6G to manage and/or alleviate pain associated with any of a wide variety of disorders, conditions, or diseases, generally those associated with opioid-responsive pain. Of particular interest is the treatment of disorders, conditions, and diseases associated with chronic pain (*e.g.*, chronic pain associated with cancer, physical injury, *etc.*).

Any of a variety of chronic pain patients can be treated according to the invention. Causes of chronic pain may be identifiable or unidentifiable. Where identifiable, the origin of pain may be, for example, of malignant, non-malignant, infectious, non-infectious, or autoimmune origin. Of particular interest is the management of chronic pain associated with disorders, diseases, or conditions that require long-term therapy, *e.g.*, chronic and/or persistent diseases or conditions for which therapy involves treatment over a period of several days (*e.g.*, about 3 days to 10 days), to several weeks (*e.g.*, about 3 or 4 weeks to 6 weeks), to several months or years, up to including the remaining lifetime of the subject. Subjects who are not presently suffering from a disease or condition, but who are susceptible to such may also benefit from prophylactic pain management using the devices and methods of the invention, *e.g.*, prior to traumatic surgery or concomitant with cancer therapy. Chronic pain amenable to therapy according to the invention may involve prolonged episodes of pain alternating with pain-free intervals, or substantially unremitting pain that varies in severity.

In general, chronic pain can be somatogenic, neurogenic, or psychogenic. Specific examples of conditions, diseases, disorders, and origins of chronic pain amenable to management according to the present invention include, but are not necessarily limited to, cancer pain (*e.g.*, metastatic or non-metastatic cancer), chronic inflammatory disease pain, neuropathic pain, post-operative pain, iatrogenic pain (*e.g.*, pain following invasive procedures or high dose radiation therapy, *e.g.*, involving scar tissue formation resulting in a debilitating compromise of freedom of

motion and substantial chronic pain), complex regional pain syndromes, failed-back pain (chronic back pain), soft tissue pain, joints and bone pain, central pain, injury (*e.g.*, debilitating injuries, *e.g.*, paraplegia, quadriplegia, *etc.*, as well as non-debilitating injury (*e.g.*, to back, neck, spine, joints, legs, arms, hands, feet, *etc.*)), arthritic pain (*e.g.*, rheumatoid arthritis, osteoarthritis, arthritic symptoms of unknown etiology, *etc.*), hereditary disease (*e.g.*, sickle cell anemia), infectious disease and resulting syndromes (*e.g.*, Lyme disease, AIDS, *etc.*), chronic headaches (*e.g.*, migranes), causalgia, hyperesthesia, sympathetic dystrophy, phantom limb syndrome, denervation, and the like. Chronic pain can be associated with any portion(s) of the body, *e.g.*,the musculoskeletal system, visceral organs, skin, nervous system, *etc.*

Specific examples of cancers that can be associated with chronic pain (due to the nature of the cancer itself or therapy to treat the cancer) include, but are not necessarily limited to lung cancer, bladder cancer, melanoma, bone cancer, multiple myeloma, brain cancer, non-Hodgkins lymphoma, breast cancer, oral cancers, cervical cancer, ovarian cancer, colon cancer, rectal cancer, pancreatic cancer, dysplastic nevi, endocrine cancer, prostate cancer, head and neck cancers, sarcoma, Hodgkins disease, skin cancer, kidney cancer, stomach cancer, leukemia, testicular cancer, liver cancer, uterine cancer, and aplastic anemia. Certain types of neuropathic pain can also be amenable to treatment according to the invention.

Chronic back pain, which is also amenable to management using the methods of the invention, is another broad category of chronic pain that can be alleviated by application of the methods of the invention. Chronic back pain is generally due to one or more of the following six causes: (i) stress on intervertebral facet joints, caused by slippage, arthritis, wedging, or scoliosis; (ii) radiculopathy, the mechanical compression of the nerve root due to bulging discs or tumors; (iii) tendonitis or tendon sprain; (iv) muscle spasm or muscle sprain; (v) ischemia, a local insufficiency in circulatory flow; and (vi) neuropathy, damage to nervous tissue of metabolic etiology or arising from cord tumors or central nervous system disease.

The methods of the invention can be used to manage chronic pain in patients who are opioid naive or who are no longer opioid naive. "Opioid naive patients" are those who have not received long-term opioid or opioid derivative therapy for pain management. "Non-opioid naive patients" are those who have received short-term or long-term opioid therapy. For example, patients who experienced intractable adverse side effects with opioids or opioid derivatives conventionally administered by an oral, intravenous, epidural, intrathecal, transdermal, subcutaneous, rectal, or inhalational route may be effectively treated delivery of M6G when administered intracerebrospinally at the dose ranges and/or low volume rates described herein.

M6G, M6G DERIVATIVES AND FORMULATIONS THEREOF

Methods for isolation of or manufacture of M6G, as well as methods of isolating or manufacturing bioactive M6G derivatives are well known in the art. For example, processes for making M6G or substituted M6G are described in U.S. Pat. Nos. 5,977,326; 5,621,087; and 5,750,381, as well as in WO 93/03051. Enzymatic processes for making M6G or substituted M6G are described in U.S. Pat. No 5,750,381.

The invention also contemplates intracerebrospinal administration of bioactive derivatives of M6G. Methods of making such bioactive M6G derivatives are described in, for example, U.S. Patent No. 5,977,326.

M6G can be provided as a base and/or pharmaceutically acceptable salt. The pharmaceutically acceptable salt embraces the inorganic and the organic salt. Representative salts include a member selected from the group consisting of hydrobromide, hydrochloride, mucate, citrate, succinate, n-oxide, sulfate, malonate, acetate, phosphate dibasic, phosphate monobasic, acetate trihydrate, bi(heplafluorobutyrate), maleate, bi(methylcarbamate), bi(pentafluoropropionate), mesylate, bi(pyridine-3-carboxylate), bi(trifluoroacetate), bitartrate, chlorhydrate, fumarate and sulfate pentahydrate.

M6G for delivery according to the invention can be provided in any of a variety of formulations compatible with intracerebrospinal delivery. The concentration of M6G in the formulation can vary from about 0.1 wt. % to about 50 or 75 wt.%. The drug can be provided in any form suitable for intracerebrospinal administration, *e.g.*, solid, semi-solid, gel, liquid, suspension, emulsion, osmotic dosage formulation, diffusion dosage formulation, erodible formulation, *etc.* Of particular interest is the administration of drug in an form suitable for administration using an external or implanted pump, particularly an implanted pump, more particularly an osmotic dosage form suitable for use with an osmotic pump.

Pharmaceutical grade organic or inorganic carriers and/or diluents suitable for intracerebrospinal delivery can be included in the formulations of the invention. Such physiologically acceptable carriers are well known in the art. Exemplary liquid carriers for use in accordance with the present invention are sterile aqueous solutions that contain no materials other than the active ingredient and water, or may contain a buffer such as sodium phosphate at physiological pH value, physiological saline or both (*i.e.*, phosphate-buffered saline). Suitable aqueous carriers may further comprise more than one buffer salt, as well as other salts (such as sodium and potassium chlorides) and/or other solutes.

The formulations comprising M6G for intracerebrospinal delivery and suitable for administration according to the invention may comprise additional active or inert components that are pharmaceutically acceptable and compatible with the active ingredient. Suitable excipients can comprise dextrose, glycerol, alcohol (*e.g.*, ethanol), and the like, and combinations of one or more thereof with vegetable oils, propylene glycol, polyethylene glycol, benzyl alcohol, dimethyl sulfoxide (DMSO), organics, and the like to provide a suitable composition. In addition, if appropriate and/or desired, the composition can comprise hydrophobic or aqueous surfactants, dispersing agents, wetting or emulsifying agents, isotonic agents, pH buffering agents, dissolution promoting agents, stabilizers, antiseptic agents and other typical auxiliary additives employed in the formulation of pharmaceutical preparations.

The formulations for delivery according to the invention can comprise additional active ingredients. For example, the formulation can comprise an opioid antagonist (*e.g.*, to further decrease the possibility of addiction or dependence, see, *e.g.*, an exemplary osmotic dosage formulation comprising an opioid agonist and an opioid antagonist is described in U.S. Pat. No. 5,866,164.

The invention as shown and described is considered to be the one of the most practical and preferred embodiments. It is recognized, however, that the departures may be made therefrom which are within the scope of the invention and that obvious modifications will occur to one skilled in the art upon reading this disclosure.

CLAIMS

What is claimed is:

1. A method for management of pain in a subject, the method comprising the steps of:

administering in a patterned fashion a therapeutically effective amount of morphine-6-glucuronide or a derivative thereof to an intracerebrospinal delivery site in a subject;

wherein said administering is effective to alleviate pain in the subject.

2. The method of claim 1, wherein said administering is substantially continuous.

3. The method of claim 1, said administering is by use of a catheter comprising a proximal end and a distal end, wherein said catheter distal end is surgically implanted at a site adjacent the intracerebrospinal delivery site and the catheter proximal end is coupled to a drug delivery device, and wherein the drug delivery device delivers morphine-6-glucuronide through the catheter and to the intracerebrospinal delivery site.

4. The method of claim 3, wherein the drug delivery device is implanted in the subject.

5. The method of claim 1, wherein the intracerebrospinal site is an intraspinal site.

6. The method of claim 5, wherein the intraspinal site is an intrathecal site.

7. The method of claim 5, wherein the intraspinal site is an epidural site.

8. The method of claim 1, wherein the intracerebrospinal site is an intracerebroventricular site.

9. The method of claim 1, wherein said administering is at a low volume rate.

10. The method of claim 9, wherein the low volume rate is from about 10 nl/day to about 1 ml/day.

11. The method of claim 1, wherein said administering is for a period of at least about 12 hours.

12. The method of claim 1, wherein pain in the subject is selected from the group consisting of: metastatic cancer pain, non-metastatic cancer pain, chronic inflammatory disease pain, neuropathic pain, post-operative pain, iatrogenic pain, complex regional pain syndromes, chronic back pain, soft tissue pain, joint and bone pain, central pain, accidental injury, arthritic pain, hereditary disease pain, infectious disease pain, chronic headache, causalgia, hyperesthesia, sympathetic dystrophy, phantom limb syndrome, and denervation.

13. A method for management of pain in a subject, the method comprising the steps of:

administering a therapeutically effective amount of morphine-6-glucuronide to an intracerebrospinal delivery site in a subject, said administering being at a low volume rate;

wherein said administering is effective to alleviate pain in the subject.

14. The method of claim 12, said administering is by use of a catheter comprising a proximal end and a distal end, wherein said catheter distal end is surgically implanted at a site adjacent the intracerebrospinal delivery site and the catheter proximal end is coupled to a drug delivery device, and wherein the drug delivery device delivers morphine-6-glucuronide through the catheter and to the intracerebrospinal delivery site.

15. The method of claim 14, wherein the drug delivery device is implanted in the subject.

16. The method of claim 13, wherein the intracerebrospinal site is an intraspinal site.

17. The method of claim 16, wherein the intraspinal site is an intrathecal site.

18. The method of claim 16, wherein the intraspinal site is an epidural site.

19. The method of claim 13, wherein the intracerebrospinal site is an intracerebroventricular site.

20. The method of claim 13, wherein said administering is patterned.

21. The method of claim 20, wherein said administering is substantially continuous.

22. The method of claim 13, wherein the low volume rate is from about 10 nl/day to about 1 ml/day.

23. The method of claim 13, wherein said administering is for a period of at least about 12 hours.

24. The method of claim 13, wherein pain in the subject is selected from the group consisting of: metastatic cancer pain, non-metastatic cancer pain, chronic inflammatory disease pain, neuropathic pain, post-operative pain, iatrogenic pain, complex regional pain syndromes, chronic back pain, soft tissue pain, joint and bone pain, central pain, accidental injury, arthritic pain, hereditary disease pain, infectious disease pain, chronic headache, causalgia, hyperesthesia, sympathetic dystrophy, phantom limb syndrome, and denervation.

25. A method of treating a subject suffering from chronic pain amenable to treatment by intracerebrospinal delivery of morphine-6-glucuronide or a derivative thereof, the method comprising the steps of:

implanting a distal end of a catheter at an intracerebrospinal site in a subject;

coupling a proximal end of the catheter to a drug delivery device to provide a delivery pathway from the drug delivery device, through the catheter proximal end, through a lumen of the catheter, and out the catheter distal end; and

delivering morphine-6-glucuronide or a derivative thereof from the drug delivery device and to the delivery site;

wherein morphine-6-glucuronide is delivered to the intracerebrospinal delivery site in an amount effective to treat pain in the subject.

26. The method of claim 25, wherein the drug delivery device is at least partially implanted.

27. The method of claim 25, wherein the intracerebrospinal site is an intraspinal site.

28. The method of claim 27, wherein the intraspinal site is an intrathecal site.

29. The method of claim 27, wherein the intraspinal site is an epidural site.

30. The method of claim 25, wherein the intracerebrospinal site is an intracerebroventricular site.

31. The method of claim 25, wherein morphine-6-glucuronide is delivered at a low volume rate.

32. The method of claim 31, wherein the low volume rate is from about 0.01 µl/day to 1 ml/day.

33. The method of claim 25, wherein said delivering is patterned.

34. The method of claim 33, wherein said delivering is substantially continuous.

35. The method of claim 25, wherein said administering is for at least about 12 hours.

36. The method of claim 25, wherein chronic pain in the subject is selected from the group consisting of: metastatic cancer pain, non-metastatic cancer pain, chronic inflammatory disease pain, neuropathic pain, post-operative pain, iatrogenic pain, complex regional pain syndromes, chronic back pain, soft tissue pain, joint and bone pain, central pain, accidental injury, arthritic pain, hereditary disease pain, infectious disease pain, chronic headache, causalgia, hyperesthesia, sympathetic dystrophy, phantom limb syndrome, and denervation.

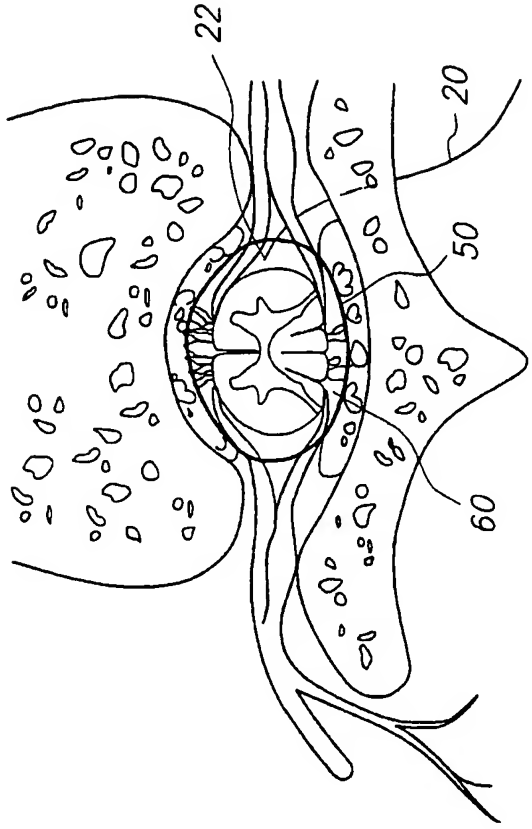


FIG. 2

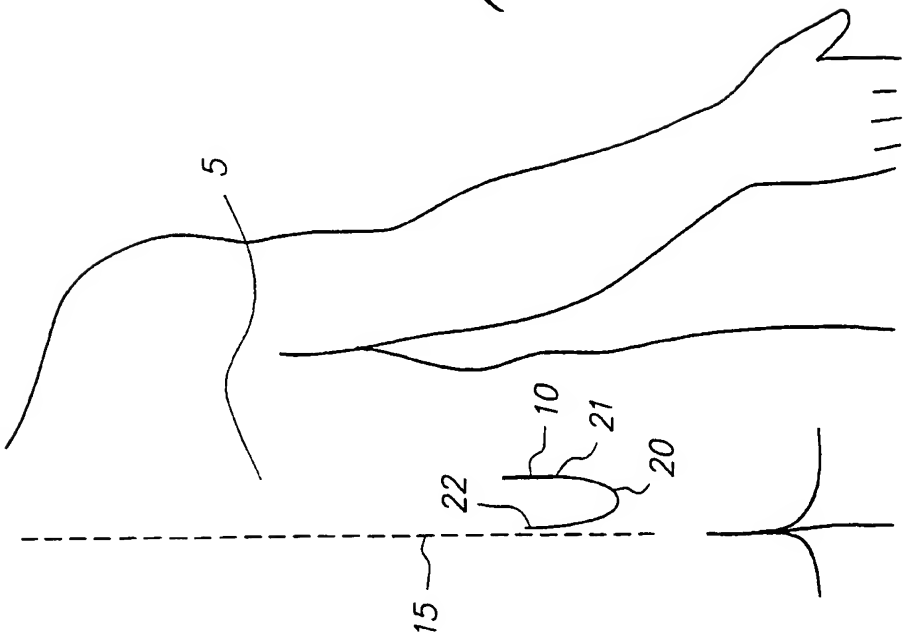


FIG. 1

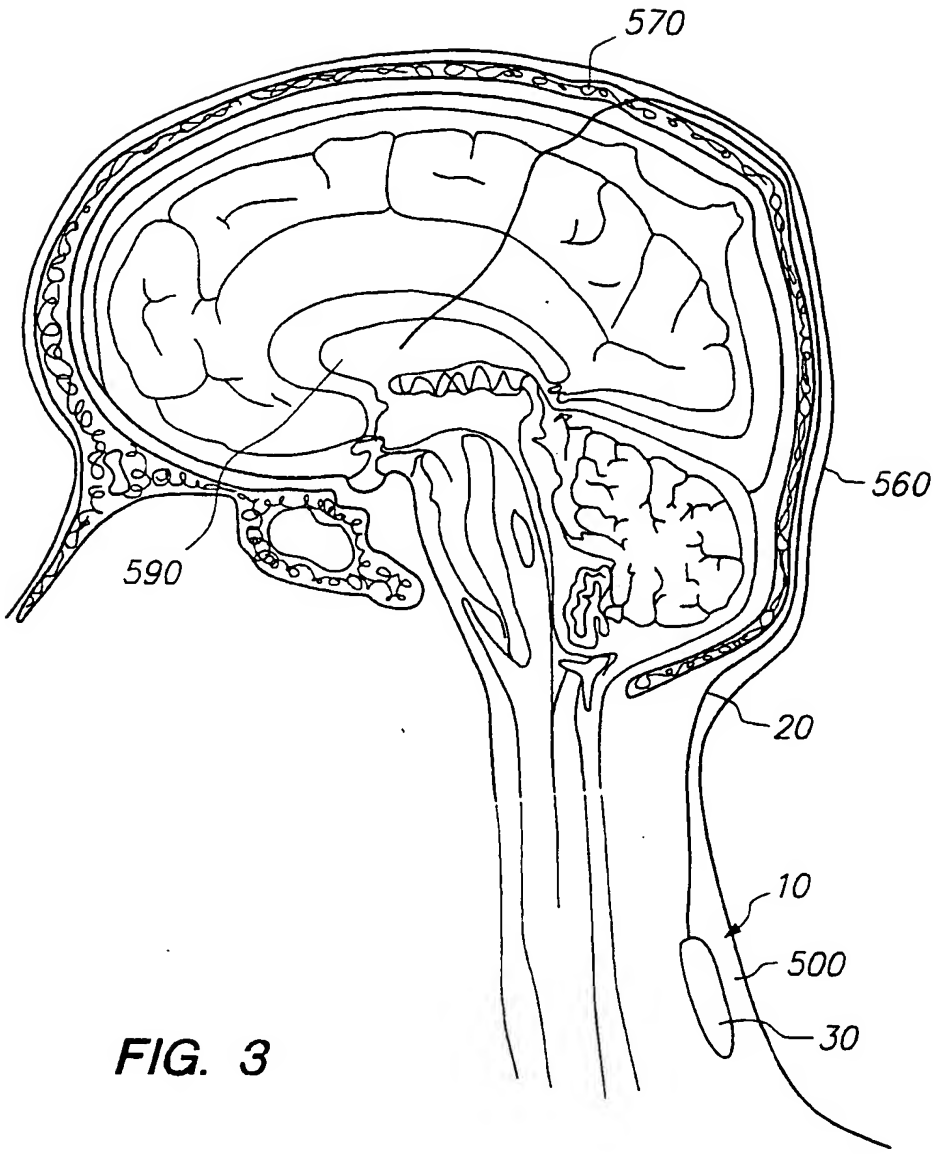


FIG. 3